

DOCKET NO.: ISIS-5429

PATENT



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:

Achim H. Krotz, et al.

Application No.: 10/806,774

Filing Date: March 23, 2004

For: METHODS FOR SYNTHESIS OF OLIGONUCLEOTIDES

Confirmation No.: Not Yet Assigned

Group Art Unit: Not Yet Assigned

Examiner: Not Yet Assigned

DATE OF DEPOSIT

*April 28, 2004*

I HEREBY CERTIFY THAT THIS PAPER IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE AS FIRST CLASS MAIL, POSTAGE PREPAID, ON THE DATE INDICATED ABOVE AND IS ADDRESSED TO THE UNITED STATES PATENT AND TRADEMARK OFFICE, P.O. BOX 1450, ALEXANDRIA, VA 22313-1450.

*Elizabeth A. McLoud*

TYPED NAME: Elizabeth A. McLoud

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Dear Sir:

INFORMATION DISCLOSURE STATEMENT

Pursuant to 37 CFR § 1.56 and in accordance with 37 CFR §§ 1.97-1.98, information relating to the above-identified application is hereby disclosed. Inclusion of information in this statement is not to be construed as an admission that this information is material as that term is defined in 37 CFR § 1.56(b).

- ☒ In accordance with § 1.97(b), since this Information Disclosure Statement is being filed either within three months of the filing date of the above-identified application, within three months of the date of entry into the national stage of the above identified application as set forth in § 1.491, before the mailing date

of a first Office Action on the merits of the above-identified application, or before the mailing date of a first Office Action after the filing of request for continued examination under § 1.114, no additional fee is required.

- ☐ In accordance with § 1.129(a), this Information Disclosure Statement is being filed in connection with ☐ the first or ☐ second After Final Submission, therefore:

☐ Certification in Accordance with § 1.97(e) is attached; or

☐ The fee of \$180.00 as set forth in § 1.17(p) is attached.

- ☐ In accordance with § 1.97(c), this Information Disclosure Statement is being filed after the period set forth in § 1.97(b) above but before the mailing date of either a Final Action under § 1.113 or a Notice of Allowance under § 1.311, or before an action that otherwise closes prosecution in the application, therefore:

☐ Certification in Accordance with § 1.97(e) is attached;

or

☐ The fee of \$180.00 as set forth in § 1.17(p) is attached.

- ☐ In accordance with § 1.97(d), this Information Disclosure Statement is being filed after the mailing date of either a Final Action under § 1.113 or a Notice of Allowance under § 1.311 but before, or simultaneously with, the payment of the Issue Fee, therefore included are: Certification in Accordance with § 1.97(e); and the submission fee of \$180.00 as set forth in § 1.17(p).

- ☐ Copies of each of the references listed on the attached Form PTO-1449 are enclosed herewith.

- ☒ Copies of references listed on the attached Form PTO-1449 are enclosed herewith
- ☒ Copies of references listed on the attached Form PTO 1449 are not required to be submitted pursuant to the June 30, 2003 recent revisions to 37 CFR § 1.98(a)(2)(i).

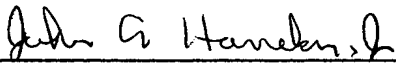
## EXCEPT THAT:

- ☒ In view of the voluminous nature of references 49-53, and the likelihood that these references are available to the Examiner, copies are not enclosed herewith.
- ☒ In accordance with § 1.98(d), copies of the following references listed on the attached Form PTO-1449 are not enclosed herewith because they were previously cited by or submitted to the U.S. Patent and Trademark Office in patent application(s) for which a claim for priority under 35 U.S.C. § 120 have been made in the instant application:
  - ☒ Copies of references 1-79 listed on the attached Form PTO-1449 were previously cited by or submitted to the Patent and Trademark Office in prior Application No. 09/032,972, filed **February 26, 1998.**

Please charge any deficiency or credit any overpayment to Deposit Account No. 23-3050. This form is submitted in duplicate.

- ☐ The relevance of those listed references which are not in the English language is as follows:
- ☒ There are no listed references which are not in the English language.

Date: April 28, 2004

  
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<b>Form PTO-1449 Modified</b>  List of Patent and Publications Cited by Applicant (Use several sheets if necessary)  U.S. Department of Commerce Patent and Trademark Office		Docket No. ISIS-5429	Application No. 10/806,774
		Applicant Achim H. Krotz, et al.	
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<b>OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)</b>			
	1	Alul, R.H. et al., "Oxalyl-CPG: a labile support for synthesis of sensitive oligonucleotide derivatives", <i>Nuc. Acid Res.</i> , <b>1991</b> , <i>19</i> , 1527-1532	
	2	Atkinson, et al., "Solid-phase synthesis of oligonucleotides by the phosphate trimer method," Ch. 3 in <i>Oligonucleotide Synthesis – A practical approach</i> , Gait (Ed.), <i>IRL Press, Washington, DC</i> , <b>1985</b> , only title and text pages 35-81 supplied	
	3	Berner, S. et al., "Studies on the role of tetrazole in the activation of phosphoramidites", <i>Nucl. Acids Res.</i> , <b>1989</b> , <i>17</i> , 853-864	
	4	Bielinska, A. et al., "Regulation of Gene Expression with Double-Stranded Phosphorothioate Oligonucleotides", <i>Science</i> , <b>1990</b> , <i>250</i> , 997-1000	
	5	Brill, W.K. et al., "Synthesis of of oligodeoxynucleoside phosphorodithioates via thioamidites", <i>J. Am. Chem. Soc.</i> , <b>1989</b> , <i>111</i> , 2321-2322	
	6	Brill, W.K.D. et al., "Synthesis of Deoxydinucleoside Phosphorodithioates", <i>J. Am. Chem. Soc.</i> , <b>1991</b> , <i>113</i> , 3972-3980	
	7	Brown, T. et al., "Modern machine-aided methods of oligodeoxyribonucleotide synthesis", <i>Oligonucleotides and Analogs</i> , Ekstein, F., ed., <i>IRL Press</i> , <b>1991</b> , <i>Chapter 1</i> , 1-24	
	8	Connolly, "Oligonucleotides containing modified bases," Ch. 7 in <i>Oligonucleotides and Analogues – A Practical Approach</i> , Eckstein (Ed.), <i>IRL Press, New York, NY</i> , <b>1991</b> , only title and text pages 155-183 supplied	
	9	Conway, et al., "Site-specific attachment of labels to the DNA backbone," Ch. 9 in <i>Oligonucleotides and Analogues – A Practical Approach</i> , Eckstein (Ed.), <i>IRL Press, New York, NY</i> , <b>1991</b> , only title and text pages 211-239 supplied	
	10	Cook, P.D., "Medicinal chemistry of antisense oligonucleotides - future opportunities", <i>Anti-Cancer Drug Design</i> , <b>1991</b> , <i>6</i> , 585-607	
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<b>OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)</b>			
	11	Copy of the EPO Supplementary European Search Report dated May 15, 2003 (EP 99 90 8511)	
	12	Dahl, B.H. et al., "Mechanistic studies on the phosphoramidite coupling reaction in oligonucleotide synthesis. I. Evidence for nucleophilic catalysis by tetrazole and rate variations with the phosphorus substituents", <i>Nucl. Acids Res.</i> , <b>1987</b> , <i>15</i> , 1729-1743	
	13	Dahl, O., "Preparation of Nucleoside Phosphorothioates, Phosphorodithioates and Related Compounds", <i>Sulfur Reports</i> , <b>1991</b> , <i>11(1)</i> , 167-192	
	14	Delgado, C. et al., "The Uses and Properties of PEG-Linked Proteins", <i>Crit. Rev. in Therapeutic Drug Carrier Sys.</i> , <b>1992</b> , <i>9</i> , 249-304	
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	16	Efimov, V.A. et al., "New efficient sulfurizing reagents for the preparation of oligodeoxyribonucleotide phosphorothioate analogues", <i>Nucl. Acids Res.</i> , <b>1995</b> , <i>23</i> , 4029-4033	
	17	Englisch, U. et al., "Chemically Modified Oligonucleotides as Probes and Inhibitors", <i>Angew. Chem. Int. Ed. Eng.</i> , <b>1991</b> , <i>30</i> , 613-629	
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	19	Horn et al., "Forks and Combs and DNA: the synthesis of branched oligonucleotides", <i>Nuc. Acids Research</i> , <b>1989</b> , <i>17</i> , pp. 6959-6967.	
	20	Horn, et al., "Solid support hydrolysis of apurinic sites in synthetic oligonucleotides for rapid and efficient purification on reverse-phase cartridges," <i>Nucleic Acids Res.</i> , <b>1988</b> , <i>16(24)</i> , 11559-11571	
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	21	Horn, et al., "Chemical synthesis and characterization of branched oligodeoxyribonucleotides (bDNA) for use as signal amplifiers in nucleic acid quantification assays," <i>Nucleic Acids Res.</i> , <b>1997</b> , 25(23), 4842-4849	
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	23	Iyer, R.P. et al., "3H-1,2-Benzodithiole-3-one 1,1-Dioxide as an Improved Sulfurizing Reagent in the Solid-Phase Synthesis of Oligodeoxyribonucleoside Phosphorothioates", <i>J. Am. Chem. Soc.</i> , <b>1990</b> , 112, 1253-1254	
	24	Iyer, R.P. et al., "The Automated Synthesis of Sulfur-Containing Oligodeoxyribonucleotides Using 3H-1,2-Benzodithiol-3-one 1,1-Dioxide as a Sulfur-Transfer Reagent", <i>J. Org. Chem.</i> , <b>1990</b> , 55, 4693-4699	
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	30	Krotz, et la., "Phosphorothioates: $\beta$ -fragmentation versus $\beta$ -silicon effect," <i>Angewandte Chemie Intl. Ed.</i> , <b>1995</b> , 34(21), 2406-2409	
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	<b>31</b>	Nielsen, J. et al., "Thermal Instability of Some Alkyl Phosphorodiamidites", <i>J. Chem. Res.</i> , <b>1986</b> , <i>S</i> , 26-27
	<b>32</b>	Ouchi, T. et al., "Synthesis and Antitumor Activity of Poly(Ethylene Glycol)s Linked to 5'-Fluorouracil via a Urethane or Urea Bond", <i>Drug Des. &amp; Disc.</i> , <b>1992</b> , <i>9</i> , 93-105
	<b>33</b>	Paul. C.H., et al., "Acid binding and detritylation during oligonucleotide synthesis," <i>Nucleic Acids Research</i> , 1996, Vol. 24, No. 15, 3048-3052.
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	<b>36</b>	Ravikumar, et al., "Efficient synthesis of deoxyribonucleotide phosphorothioates by the use of DMT cation scavenger," <i>Tetrah. Letts.</i> , <b>1995</b> , <i>36(37)</i> , 6587-6590
	<b>37</b>	Secrist, J.A. et al., "Synthesis and Biological Activity of 4'-Thionucleosides", <i>10th International Rountable: Nucleosides, Nucleotides and their Biological Applications</i> , <b>Sept. 16-20, 1992</b> , <i>Abstract 21</i> , Park City, Utah, 40
	<b>38</b>	Sekine, M. et al., "Synthesis and Properties of <i>S,S</i> -Diaryl Nucleoside Phosphorodithioates in Oligonucleotide Synthesis", <i>J. Org. Chem.</i> , <b>1979</b> , <i>44(13)</i> , 2325-2326
	<b>39</b>	Septak, "Kinetic studies on depurination and detritylation of CPG-bound intermediates during oligonucleotide synthesis," <i>Nucleic Acids Res.</i> , <b>1996</b> , <i>24(15)</i> , 3053-3058
	<b>40</b>	Sinha, N.D., "Large-Scale Oligonucleotide Synthesis Using the Solid-Phase Approach," Chapter 18, pp. 437-463, from <i>Methods in Molecular Biology</i> , Vol. 20: <i>Protocols for Oligonucleotides and Analogs</i> , Edited by S. Agrawal, <b>1993</b> Humana Press Inc., Totowa, NJ.
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	41	Sproat, et al., "2'-O-methyloligoribonucleotides: Synthesis and applications," Ch. 3 in <i>Oligonucleotides and Analogues – A Practical Approach</i> , Eckstein (Ed.), IRL Press, New York, NY, 1991, only title and text pages 49-86 supplied	
	42	Sproat, et al., "Solid-phase synthesis of oligodeoxynucleotides by the phosphotriester method," Ch. 4 in <i>Oligonucleotide Synthesis – A Practical Approach</i> , Gait (Ed.), IRL Press, Washington, DC, 1985, only title and text pages 83-115 supplied	
	43	Vu, H. et al., "Internucleotide Phosphite Sulfurization with Tetraethylthiuram Disulfide. Phosphorothioate Oligonucleotide Synthesis via Phosphoramidite Chemistry", <i>Tetrahedron Letts.</i> , 1991, 32, 3005-3008	
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	46	Xu, Q. et al., "Efficient introduction of phosphorothioates into RNA oligonucleotides by 3-ethoxy-1,2,4-dithiazoline-5-one (EDITH)", <i>Nucl. Acids Res.</i> , 1996, 24, 3643-3644	
	47	Xu, Q. et al., "Use of 1,2,4-dithiazolidine (DtsNH) and 3-ethoxy-1,2,4-dithiazoline-5-one (EDITH) for synthesis of phosphorothioate-containing oligodeoxyribonucleotides", <i>Nucl. Acids Res.</i> , 1996, 24, 1602-1607	
	48	Yau, E.K. et al., "Synthesis of Dinucleoside and Dinucleotide Phosphorodithioates Via a Phosphotriester Approach", <i>Tetrahedron Letts.</i> , 1990, 31, 1953-1956	
*	49	Ausubel et al. (eds.), <i>Current Protocols in Molecular Biology</i> , Current Publications, 1993	
*	50	Eckstein, F. (ed.), <i>Oligonucleotides and Analogues A Practical Approach</i> , IRL Press, New York, 1991	
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\* A copy of these references will not be forwarded to the U.S. Patent and Trademark Office since they are believed to be too voluminous and easily obtainable by the Examiner.

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*	51	Greene and Wuts, <i>Protective Groups in Organic Synthesis</i> , 2d. Ed., John Wiley & Sons, New York, 1991	
*	52	Sambrook, J. et al. (eds.), <i>Molecular Cloning, A Laboratory Manual</i> , Second Ed., Cold Spring Harbor Laboratory Press, 1989	
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<b>Examiner Initial</b>		<b>Document No.</b>	<b>Date</b>	<b>Name</b>	<b>Class</b>	<b>Subclass</b>	
	54	RE 34,069	09/15/92	Köster et al.	536	27	
	55	3,687,808	08/29/72	Merigan et al.	195	28	
	56	4,415,732	11/15/83	Caruthers et al.	536	27	
	57	4,458,066	07/03/84	Caruthers et al.	536	27	
	58	4,500,707	02/19/85	Caruthers et al.	536	27	
	59	4,517,338	05/14/85	Urdea et al.	525	54	
	60	4,668,777	05/26/89	Caruthers et al.	536	27	
	61	4,725,677	02/16/88	Köster et al.	536	27	
	62	4,816,571	03/28/89	Andrus et al.	536	27	
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	65	5,132,418	07/21/92	Caruthers, et al.	536	25.34	
	66	5,151,510	09/29/92	Stec et al.	536	27	
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	68	5,210,264	05/11/93	Yau	558	167	
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Examiner Initial		Document No.	Date	Name	Class	Subclass
	69	5,212,295	05/18/93	Cook	536	26.7
	70	5,216,141	06/01/93	Benner	536	27.13
	71	5,292,875	03/08/94	Stec et al.	536	25.33
	72	5,548,076	08/20/96	Froehler, et al.	536	25.34
	73	5,554,746	09/10/96	Ravikumar, et al.	540	200
	74	5,614,621	03/25/97	Ravikumar, et al.	536	35.34
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### FOREIGN PATENT DOCUMENTS

Examiner Initial		Document No.	Date	Country	Translation	
					YES	NO
	79	0 294 196	12/07/88	EPO		

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